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1645	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No. 09/512,082	Applicant(s) Neri et al
	Examiner Portner	Art Unit 1645

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jan 3, 2002 and April 17, 2001.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 14-17 and 19-48 is/are pending in the application.

4a) Of the above, claim(s) 14-17 and 35 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 19-34 and 36-48 is/are rejected.

7) ☒ Claim(s) 28 and 36-47 is/are objected to.

8) ☒ Claims 14-17 and 19-48 are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence letter*

DETAILED ACTION

New claims 36-48 have been added.
Claims 14-17 and 35 are withdrawn.
Claims 14-17, 19-35, 36-48 are pending.
Claims 19-34, 36-48 are under consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections/Rejections Withdrawn

2. Claims 19 and 29-34 rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101, in light of the claims to recite a specific active voice methods step.

3. Claim 19 rejected under 35 U.S.C. 112, second paragraph, for reciting at least two different methods, specifically "diagnosis" and "therapy of tumors and diseases", in light of the amendment of the preamble of the claim to recite intended use of the method.

4. Claim 19 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "characterized by" and "characteristic epitope", in light of the amendment of the claim to delete these phrases and insertion of the word --comprising--.

5. Claims 20-34 rejected under 35 U.S.C. 112, second paragraph for depending from canceled claim 1 and potentially reciting the phrase "improved affinity to said ED-B epitope", in light of the amendment of the claim to recite the phrase "specific, high affinity".

6. Claims 20-34 rejected under 35 U.S.C. 112, second paragraph for intending to recite the phrase "said ED-B epitope" which lacks antecedent basis in claim 1, has been obviated through the deletion of this phrase from the claims.

7. Claim 34 rejected under 35 U.S.C. 112, second paragraph for depending from claim 28, which recites the phrase "is represented by a photosensitizer and a radio nucleotide", in light of the amendment of claim 28 to recite the word --comprising-- and deletion the phrase "is represented by a photosensitizer and a radio nucleotide".

8. Claim 19 rejected under 35 U.S.C. 102(b) as being anticipated by Carnemolla et al (1996, reference provided in Applicant's 1449), in light of the amendment of claim 19 to recite the methods step of administering an antibody to a patient.

9. Claims 19, 20, 25, 29, 32 rejected under 35 U.S.C. 102(a) as being anticipated by Mariani et al (December 15, 1997), in light of Applicant's traversal stating that the claims do not encompass antibodies with the binding specificity of monoclonal BC-1.

10. Claims 26, 27 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mariani et al (December 15, 1997) as applied to Claims 19, 20, 25, 29, 32 above, in view of Goldberg (US Pat. 5,776,095; filing date June 1, 1995), in light of Applicant's traversal stating that the claims do not encompass antibodies with the binding specificity of monoclonal BC-1.

Objections and Rejections Maintained

11. The disclosure objected to because of the following informalities: The instant specification, page 15, lines 1-11, has been amended through submission of an Amendment of the Specification, dated January 3, 2002, but this paragraph still recites a hyperlink to the Internet. This is not permitted in Official Patent Application. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. **See MPEP § 608.01.** Appropriate correction is required.

12. Objection to the Brief Description of the Several Views of the Drawing(s) is maintained for reasons of record as the figures show more than one view where are not briefly referred to and described in the brief description of the drawing(s) as set forth in 37 CFR 1.74. Drawings: See 37 CFR 1.81, 1.83-1.85, and MPEP § 608.02. The Brief Description of the Drawings and the figures shown do not evidence clear labels and description of the contents of the figures.

a. Figures 1A & 1B should be recited and briefly described.
b. Figures 2A & 2B should be recited and briefly described.
c. Figures 3 A,B &C should be recited and briefly described.
d. Figures 4 A,B &C should be recited and briefly described
e. Figure 6 refers to only a single SEQ ID NO, the figure should define the three sequences shown and therefore should be assigned 3 SEQ ID NOS.
f. Figure 7, each frame (A-H) should be labeled and briefly described. Figure 7 shows several abbreviations. These abbreviations should be defined in the Brief Description of the Drawings. Clarification of the abbreviations is requested.
g. Figure 9,each frame (A-C) should be labeled and briefly described.
h. Figure 10,each frame (A-D) should be labeled and briefly described.
i. Figure 11, each frame (A-L) should be labeled and briefly described.
j. Figure 12,each frame (A-L) should be labeled and briefly described.
k. Figure 13,each frame (A-B) should be labeled and briefly described.
l. Figure 14, each frame (A-C) should be labeled and briefly described.
m. Figure 15,each frame (A-B) should be labeled and briefly described.

13. Claim 1 rejected under 35 U.S.C. 112, second paragraph for reciting the abbreviation ED-B, is maintained for reasons of record in paper number 7; this rejection could be obviated through amendment of the claim to recite the meaning for the letters "ED".

14. Claim 31 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "associated with ocular angiogenesis", because the patient has not been defined to be a patient with an ocular problem, and therefore claim 31 does not further limit the method of claim 30 as they both recite the same methods step.

15. Claims 19, and 29-34 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: providing a conjugate, a subject to whom the reagent is

administered and a correlation step with the preamble of the claim, in light of fact that no correlation between what is administered and what the recited intended use of each method has been set forth in the claims.

16. Claims 20-22, and new claims 36-38 are rejected under 35 U.S.C. 102(b), as previously applied to claim 19 as being anticipated by Carnemolla et al (1996, reference of record), for reasons of record in paper number 7.

17. Claims 19, 20-23, 25, 29-31, 32, 36-39, 41-43 and new claim 48 are rejected under 35 U.S.C. 102(a) as being anticipated by Neri et al (WO97/45544, reference provided in Applicant's 1449) for reasons of record in paper number 7.

18. Claims 19-20,25, 29, 36-38, 41-43,47- 48 as previously applied to claim 20 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Thorpe et al (US Pat. 6,093,399) for reasons of record in paper number 7.

19. Claims 26-27 and 33 under 35 U.S.C. 103(a) as being unpatentable over Neri et al (WO97/45544), in view of Goldenberg (US Pat. 5,776,095; filing date June 1, 1995), , for reasons of record.

20. Claima 24, and new claim 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neri al) as applied to claims 19, 20-23, 25, 29-30 above, in view of Fritzberg et al (US Pat. 5,976,535; filing date June 1995), for reasons of record.

Information Disclosure Statement

21. The information disclosure statement filed November 15, 2000 has been considered.

Allowable Subject Matter

22. Claims 28, 45-46 are objected to as being dependent upon a rejected base claim, or are rejected under 35 USC 112, second paragraph, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, as well as obviating the objection (mis-spelled word) and rejection under 35 USC 112 second paragraph set forth below.

Response to Arguments

23. The rejection of claims 20-22 and new claims 36-38, as previously applied to claim 19 rejected under 35 U.S.C. 102(b) as being anticipated by Carnemolla et al (1996) is traversed on

the grounds that the antibodies of Carnemolla et al "do not exhibit an affinity in the subnanomolar range"

24. It is the position of the examiner that Carnemolla et al (1996) disclose the instantly claimed invention directed to an anti-ED-B domain antibody conjugated to a molecule that is a photoactivatable molecule (see page 398, col. 2, paragraph 2, Flag epitope which is a phosphorylable tag, and therefore a photoactive molecule; page 400, col. 1, paragraph 3 and 4 "Binding of CGS-1 and -2 to B-FN was inhibited by the recombinant ED-B domain"; page 404, col. 1, paragraph 3, first sentence; results, col. 1, page 400, paragraph 3; Figure 1, page 398, top of page; see page 399, Figure 2). Claims 20-22 do not require the specific binding affinity to be in the subnanomolar range as argued by Applicant, but even if they did, as in newly submitted claims 36-38, it is the position of the examiner that a single antibody will bind to a ED-B molecule which has a molecular weight of a subnanomolar range, specifically in a molecule with a relative molecular weight measured in kilodaltons would result in a molar concentration in the subnanomolar range. The recitation of a range of binding specificities for a single antibody is confusing. See new grounds of rejection under 35 U.S.C. 112, second paragraph set forth below. Applicant's arguments are not commensurate in scope with the instantly claimed invention.

25. The rejection of claims 19, 20-23, 25, 29-31, 32, 36-39, 41-44 and new claim 48 under 35 U.S.C. 102(a) as being anticipated by Neri et al (WO97/45544, reference provided in Applicant's

1449), is traversed on the grounds that "the references do not disclose an antibody which exhibits "high affinity" for the ED-B domain."

26. It is the position of the examiner that Neri et al disclose the instantly claimed invention. Claims 19, 20-23, 25, 29-32 do not require the antibody to evidence subnamomolar binding affinity, and claims 36-39, 41-44 and 48 are unclear as to how a range of binding affinities can exist for a single antibody that binds specifically to a single molecule with a relative molecular weight that is measured in kilodaltons. A antibody that binds to an epitope with a relative molecular weight measured in Daltons would result in the antibody conjugate binding a sequence that would evidence a molar concentration in the subnanomolar range.

Additionally, one of the disclosed conjugates was administered in vivo (mice, see page 36, lines 12-18) and imaged (detection method, instant claim 19) using an infrared mouse imager (a type of irradiation, see page 36, line 19). Injected conjugates detected the presence of tumor cells visualized at a macroscopic level (see page 38, line 29; page 37, lines 11-13) and also resulted in tumor clearance (treatment, instant new claim 48). The reference anticipates the now claimed conjugates and methods. Applicant's arguments are not commensurate in scope with the instantly claimed invention. The rejection is maintained for reasons of record in paper number 7.

27. The rejection of claims 19-20,25, 29, 36-38, 41-43, 47-48 as previously applied to claim 20 and 29 under 35 U.S.C. 102(e) as being anticipated by Thorpe et al (US Pat. 6,093,399) is

traversed on the grounds that Thorpe et al does not disclose an antibody that is specific for the ED-B domain, and asserts that monoclonal antibody BC-1 is not specific for the ED-B domain. 28. It is the position of the examiner that the disclosure of Thorpe et al (US Pat. 6,093,399) is not limited to the utilization of monoclonal antibody BC-1 as the binding agent for the tumor associated fibronectin isoform (ED-B) as Thorpe et al discloses and claims a genus of antibodies with this binding specificity (see Thorpe et al , col. 7, lines 14-24; col. 8, lines 9-12), that are combined with a radioactive label (RIA, see col. 13, line 22-23), a fluorescent label (see col. 13, line 23-24) or combined with radiotherapy (see col. 14, lines 63-66).

While Thorpe et al provides BC-1 as an example of an antibody that binds Tumor associated isoforms of fibronectin, the patent does not limit the claimed binding agents to monoclonal antibody BC-1. The bispecific antibodies are specific for fibronectin tumor associated isoform, otherwise known as ED-B domain . The bispecific conjugate antibodies are disclosed as agents for coagulation and are also disclosed to be radio labeled (see col. 49, lines 17-27; col. 49, lines 61-67; col. 76, lines 33-40), combined with fluorescently activated labels (see col. 13, line 24), formulated for administration to the eye, skin or parenterally (see col. 69, lines 3-67 and col. 70, lines 4, 10-50) and used together in combination therapy.

Thorpe et al '399, is herein applied to new claims 36, 41-42 and 48 based upon the lack of clarity of the combination of claim limitations set forth in claim 36 (see rejection under 35 U.S.C.

112, second paragraph below). The rejection is maintained for reasons of record in paper number 7, paragraphs 22-23.

29. The rejection of claims 26-27 and 33 under 35 U.S.C. 103(a) as being unpatentable over Neri et al (WO97/45544), in view of Goldenberg (US Pat. 5,776,095; filing date June 1, 1995) is traversed on the grounds that there is no motivation to modify the composition of Neri et al, and the antibody conjugates of Neri et al do not evidence high affinity.

30. It is the position of the examiner that the conjugate antibodies of Neri et al specifically bind to ED-B in a sample, are taught for in vivo imaging (see page 16, paragraphs 1-2) and for treating disease (see page 16, paragraphs 3-4) and therefore were able to show high affinity for the antigen to which they were raised. Neri et al's antibodies specifically bound to the ED-B domain present in a tissue sample. The antibody conjugates were taught to comprise an antibody with a radio nucleotide. Clearly there is motivation provided by the art to use an alpha or beta emitter radionucleotide, specifically the use of astatine-211 or bismuth-212 because Goldenberg shows the use of antibody conjugates (see col. 9, lines 8-64; especially lines 36-37) that comprise alpha and beta emitters to be useful in cancer therapy, teaches that alpha and beta radionucleotides are effective in the formulation of conjugates for clinical applications, wherein the emitters are astatine or bismuth radionucleotides. Neri et al teaches the antibody conjugates are useful in targeting the ED-B domain associated with tumor cells (see page 1, paragraph 1). Goldenberg teaches Astatine-211 and Bismuth-212 as means for localization and therapy of abnormal tissues

and which evidence a longer half life than that of a gamma emitter, thus defining a radio nucleotide with a longer half life which could remain localized at the site of the abnormal tissue and alpha and beta emitters are also known to cause reduced genetic damage as compared to gamma emitter radionucleotides. Substituting an alpha or beta emitter (Goldenberg) in the place of a gamma emitter radio nucleotide (Neri et al) provide advantages of increased half life and the likelihood of reduced random genetic damage to normal tissues in the vicinity of the abnormal tissue to which the radio nucleotide/antibody conjugate would bind. The rejection is maintained for reasons of record in paper number 7.

31. The rejection of claim 24, and new claim 40 under 35 U.S.C. 103(a) as being unpatentable over Neri al) as applied to claims 19, 20-23, 25, 29-30 above, in view of Fritzberg et al (US Pat. 5,976,535; filing date June 1995) is traversed on the grounds that there is no motivation to modify the composition of Neri et al, and the antibody conjugates of Neri et al do not evidence high affinity.

32. It is the position of the examiner that the conjugate antibodies of Neri et al were able to specifically bind to ED-B in a sample, and therefore were able to show high affinity for the antigen to which they were raised. The antibodies directed against the ED-B domain bound to an ED-B epitope in a mixture of antigens (tissue sample). Therefore the antibodies of Neri et al bound with high affinity for the ED-B domain. The antibody conjugates were taught to comprise an antibody with a radio nucleotide. Clearly there is motivation provided by the art to use conjugates of an

antibody with a photosensitizer specifically the use of tin(IV) choline e6. Fritzberg et al teach the use of antibody conjugates that comprise tin(IV) choline e6 (col. 28, line 2) photosensitizer in an analogous art for the purpose of producing conjugates useful in photodynamic therapy that are readily incorporated into the conjugate molecule (see col. 27, lines 16-24). Photosensitizer molecules are taught to have longer half lives, generally up to two months (see col. 28, lines 24-25), evidence a strong absorption band between 600 and 700 nm and provide a means for enhanced performance of photodynamic therapy protocols (see col. 27, lines 58-63). Fritzberg et al teach means and methods of utilizing a photosensitizer that facilitate target cell specific accretion of photosensitizing agent and obviate the necessity for a recipient to avoid direct sunlight (see col. 28, lines 30-36). The realized advantage to the patient (recipient) of the conjugate that comprises the photosensitizer need not avoid direct sunlight and may even obtain a residual benefit from exposure to sunlight which is unlike other previously known photosensitizer (see Fritzberg, col. 28, lines 30-36).

New Claim Limitations/Amendment of the Specification/New Grounds of Objection/Rejection

Claim Objections

33. Claims 36-47 are objected to because of the following informalities: The claims recite the term "subnamomolar" which appears to be a mis-spelled word. Appropriate correction is required.

Sequence Letter

34. APPLICANT IS GIVEN THE time limit set for THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

35. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a) (1) and (a) (2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

36. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.136. In no case may and applicant extend the period of response beyond the six month statutory period and the response period is the time set in this action. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

37. **Specifically:**

a. see page 19, lines 26-27, shows an amino acid and a nucleic acid sequences and were assigned two SEQ ID Nos. The first appearing sequence is an amino acid sequence and the second sequence being a nucleic acid sequence. The two SEQ ID Nos assigned are SEQ ID NO 25 and 26 respectively, but SEQ ID NO 25 is a nucleic acid sequence and SEQ ID No 26 is an amino acid sequence, therefore the sequences for the sequences should be SEQ Id No 26, and 25

respectively and not SEQ Id No 25-26, respectively. The narrative inserted is unclear with respect to the order in which the sequence appear.

b. Original descriptive support for the changes to Table 1 could not be found in the instant specification and constitutes New Matter. Applicant is requested to point out where in the instant specification support was found for making the sequence changes inserted into Table 1 to obviate this rejection.

Claim Rejections - 35 U.S.C. § 112

38. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 19 has been amended to set forth a method of diagnosing a tumor or disease through the administration of "an antibody". While the antibody is specific for the ED-B domain of fibronectin, the antibody is not detectable, and therefore not diagnostic for any type of tumor or disease. Antibodies specific for the ED-B domain would bind specifically to their target, but without some type of means of measuring the binding to the ED-B domain, no diagnosis could be carried out. The instantly claimed method is not enabled for diagnosising the presence of a tumor or disease because the binding or non-binding of the antibody to the ED-B domain is not distinguishable. No signal would be generated to indicate the presence of a tumor or disease as the antibody does not comprise a signal generating molecule; the antibody administered to a patient is not a diagnostically detectable antibody and therefore the instant method is not enabled.

39. Claims 29-34 and claim 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 29-34 and new claim 48 set forth methods of treating various conditions through administering a conjugate of an antibody and a molecule which induces blood coagulation and or/blood vessel occlusion.

While the antibody is specific for the ED-B domain of fibronectin, the molecule which induces blood coagulation and or/blood vessel occlusion is not so claimed as to only function upon binding or incorporation into a tumor cell or diseased cell. The ED-B domain is known to be expressed in normal tissues (see WO97/45544, page 4, line 2 "normal cells") of a fetus, and is considered to be abnormally expressed in tumors. The ED-B domain is also expressed during wound healing and inhibition of wound healing would not serve to treat the wound (see WO97/ page 4, line 4).

The instantly claimed method , would induce blood coagulation and or/blood vessel occlusion at the site of administration which is not the disease associated cite. Premature blood coagulation and or/blood vessel occlusion prior to reaching the disease site would cause systemic blood circulation problems and non-treatment of disease. Induction of blood coagulation and or/blood vessel occlusion is not limited to be at the cite of the tumor or disease, thus inducing negative, undesirable blood coagulation and or/blood vessel occlusion at the site of administration.

The amount of antibody conjugate administered is not an amount that would serve to treat a disease and the patient to which the conjugate is administered has not been defined to be a patient with a tumor or a type of undesirable angiogenesis.

Administration of the antibody conjugate to a patient that does not, for example, have a tumor, would not be treated by the administered antibody conjugate. A patient with a tumor that does not receive an amount of antibody conjugate that would serve to treat disease also would not be treated for tumor associated angiogenesis.

The instantly claimed methods of treatment are not enabled for treating a tumor or disease that does not express an ED-B domain associated tumor; all tumors do not express ED-B

as a tumor marker, as well as are not enabled for treatment of patients that do not have a tumor that expresses ED-B, nor enabled for the administration of a blood coagulation and/or blood vessel occlusion to any site of administration and result in treatment of the tumor or disease. The instant methods are not enabled.

40. Claims 36-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36-47 recites the phrase "said affinity is in the subnanomolar range". How can a single antibody have a range of binding affinities which each antibody has a single binding specificity for a single molecule? The claims are unclear with respect to the binding affinity of the claimed conjugate as a single antibody (scFv polypeptide binding agent) only binds to a single molecule (single epitope/two molecules of the same epitope for an antibody) which has a molecular weight and would be in the subnanomolar range. Do claims 36-47 seek to set forth a binding assay claim limitation for the antibody in the claimed conjugate, or do the claims only require the relative molecular weight of the single molecule to which the claimed conjugate binds to be in the subnanomolar range of weight? The claimed invention is unclear as an antibody only has a single binding affinity for a single type of molecule and the recitation of range of affinities for a single antibody for the recited ED-B domain introduces confusion because what the conditions are that altered binding affinity of the claimed conjugate are not set forth in the claims, nor are the molecules which would evidence a range of molecular weights resulting in different subnanomolar binding affinities for a single conjugate has not been set forth in the claims. The claims are unclear with respect to the affinity of the claimed conjugate through the recitation of a range of affinities while only claiming a single conjugate molecule that would be expected to evidence only a single binding affinity for the molecule to which it is specific. The ED-B epitope is a molecule with a relative molecular weight in a subnanogram range of molecular weight.

Conclusion

41. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

42. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Peters et al (August 1996) is cited to show antibodies to ED-B that bind to fibronectin without glucanase pretreatment (see Figure 8, Frame C, page 142, and ledger narrative). EP0760679 B1 is cited to show a monoclonal antibody that binds to human melanoma cells (see paragraph [0099], page 12. Vartio et al (1987) is cited to show antibodies that bind to the ED sequence of fibronectin and referred to as "The DH antibody" (see abstract, Figure 1, page 422, col. 2; page 423, all of col. 1) . Ueda et al (186) is cited to show radiolabelled antibodies that bind to tumor associated fibronectin (see summary, page 261, and page 265, paragraphs 1-2); Neri et al (November 1997) is cited to show single antibody fragments that bind to ED-B, see Results section,page 1271, col. 2).

43. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

September 4, 2002

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Application No.: 09/512,082

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [ ] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: Unclear narrative to identify sequences and New Matter.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [ ] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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